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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/800,031
Filing Date: March 15, 2004
Appellant(s): BIELSKI ET AL.

Paul M. Zagar
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 09/28/11 appealing from the Office action mailed 11/09/10.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 1-66 are pending, claims 61-65 remain withdrawn and claims 1-60 and 66 are rejected and on appeal.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the

subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

US 4,772,473	Patel et al	09-1988
US 2003/0180359	Vergnault et al	09-2003
US 4,792,452	Howard et al	12-1988
US 5,415,871	Pankhania et al	05-1995

(9) Grounds of Rejection

MAINTAINED REJECTIONS

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-60 and 66 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 4,772,473 ('473) in view of US 2003/0180359 ('359) or US 4,792,452 ('452) and US 5,415,871 ('871).

The instant claims are drawn to an orally administrable formulation for administering nitrofurantoin to a patient in need thereof which comprises: a first component being a controlled release form and a second component being an immediate release form, wherein (a) said first component comprises nitrofurantoin monohydrate, sodium alginate, alginic acid and hypromellose; (b) said second component comprises macrocrystalline nitrofurantoin; and (c) said formulation provides a therapeutically effective combination of said nitrofurantoin monohydrate and said macrocrystalline nitrofurantoin.

- '473 teaches all the limitations of the instant claims except the first component controlled release excipients. '473 teaches a combination sustained/rapid release pharmaceutical capsule for oral administration of nitrofurantoin comprising a first particulate of nitrofurantoin and sustained release excipients (i.e., PVP and carboxyvinyl polymer) and a second particulate comprising macrocrystalline nitrofurantoin (abstract, col.5, lines 35-39 and col. 8, lines 18-27). The first particulate comprising nitrofurantoin is nitrofurantoin monohydrate (examples, col. 10, lines 45 and 57-67) (according to the limitations of claim 1).
- '473 teaches that the components are "particulate mixtures" such as powders, granules, etc. (col. 3, lines 46-47), a sustained release mixture of nitrofurantoin monohydrate with the sustained release polymer (first particulate) which are uniformly mixed together with any other pharmaceutical carriers, a second particulate mixture of macrocrystalline nitrofurantoin mixed with any other pharmaceutical carriers can be added to the layers to aid in the flow of the

particulate mixture into the dosage form for rapid release (col. 8, lines 47-67) and that the first and second components can be layered or enclosed in smaller units within the capsule shell containing the entire dosage form (abstract, col. 4, lines 1-19; col. 6, lines 22-26; col. 9, lines 41-col. 10, lines 30; Example 1) (meeting the limitations of claims 2, 4-10, 41, 43-52, and 54-60).

- '473 teaches first particulate comprising nitrofurantoin is nitrofurantoin monohydrate (examples, col. 10, lines 45 and 57-67) in amounts of 150-161.4 mg and also generally 50-1000 mg, preferably 100-400, more preferably 150-250mg per capsule (col.6, lines 18-51) (meeting the limitations of claims 11-13). '473 teaches the second particulate comprising macrocrystalline nitrofurantoin is amounts of 10-200 mg, preferably 25-100 mg (col. 6, lines 6-8) (meeting the limitations of claims 14-16) and thus the ratios of the drugs overlap with those instant claimed in claims 30, 33, 37 and 40).
- '473 teaches the sustained release polymers in amount of 5-86% and 4-40%, etc. (col. 7, lines 5-7 and col. 8, lines 29-30) (meeting the limitations of claims 17-26, 30 and 37).
- '473 teaches diluents, fillers, coloring agents, etc. (col. 8, lines 48-col. 9, lines 6) and coating the dosage (col. 9, lines 28-39) and about 5% of colorants such as zinc stearate (Examples) (meeting the limitations of claims 28-29, 31-32, 36, 38-39 and 66).
- Stearic acid, talc, lactose, sucrose, etc. are all taught as excipients (col. 8, lines 48-col. 9, lines 6) (meeting the limitations of claims 34-35).

'473 does not teach a tablet (instant claims 3, 42, and 53), exact percentages instant claimed, or the sustained release polymers of the first component of alginic acid, sodium alginate and hydroxypropylmethylcellulose (instant claims 1 and 27), but does teach a first particulate comprising nitrofurantoin monohydrate and sustained release polymers/excipients and overlapping percentages.

- '359 teaches multi-layer dosage forms including caplets, tablets, etc. [0020] (instant claims 3, 42, and 53). '359 also teaches that controlled release polymers/excipients are included in the active layer from 1-75% by weight and preferably 5-65% by weight include PVP, HPMC (i.e. hypromellose), carboxyvinylpolymers, alginic acid and derivatives such as sodium alginate [0038, 0046]. '359 teaches specifically preferred polymeric substances for the active layer include a combination of one or more of a) and b), where a) includes HPMC and b) includes alginic acid, sodium alginate [0041]. '359 goes on to teach preferably 40-63% by weight specifically for HPMC and the viscosity increasing polymers (i.e. alginic acid and sodium alginate) 3-20% by weight which all overlap with the instant claimed weight % and ratios [0046] (meeting the limitations of instant claims 1, 17-27, 30 and 37).
- '452 teaches a controlled release formulation comprising a pharmaceutical and polymers of alginic acid such as sodium alginate and HPMC in an amount of up to 35% or 3-15% by weight (abstract, col. 1, lines 11, col. 3, lines 15-60 and Examples). '452 teaches that mixtures of the same or different alginic acid

derivatives can be used in amounts of 15-45% (col. 3, lines 18-20 and 28-30) (meeting the limitations of instant claims 1, 17-27, 30 and 37). While '871 teaches that polymer having sustained release properties can be replaced with one or more sustained release polymers including sodium alginate or alginic acid (col. 4, lines 13-20) and that the can be formulated into any solid dosage such as a gelatin capsule, tablet, etc. (col. 6, lines 29-34) (instant claims 3, 42, and 53).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine '473 in view of '359 or '452 and '871. A skilled artisan would know how to substitute the sustained release polymers and/or tablet form of '359 or '452 and '871 for the polymers and/or capsule in the product of '473 with predictable results. Such a substitution of one sustained release polymer for another sustained release polymer is within the purview of the skilled artisan and would yield predictable results. Furthermore, adjusting the percent of a compound in the formulation is simple optimization and known to a skilled pharmacologist. One of ordinary skill in the art would know how to optimize the ranges of '473 and '359 or '452 and '871, as the MPEP 2144.05 states: "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also

Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969).

(10) Response to Argument

(A) Appellants argue that '473 teaches "a nitrofurantoin formulation containing the "necessary" sustained release ingredients polyvinylpyrrolidone and carboxyvinylpolymer" and "one of ordinary skill in the art would not have substituted the "necessary" (absolutely needed) controlled release excipients taught in the '473 patent with the instantly claimed controlled release excipients" (brief pages 13 and 15). The Examiner respectfully points out that '473 is not relied upon alone but in combination with '359 or '452 and '871 and '473 is only relied upon for its teaching of a sustained release/rapid release oral dosage form comprising a first layer of nitrofurantoin monohydrate and sustained release substituents and a second layer of macrocrystalline nitrofurantoin, and not for its teaching of the instant claimed sustained release excipients (abstract, col. 4, lines 43-55; col. 10, lines 57-60). '473 in its full disclosure teaches that PVP and carboxyvinylpolymer "are substituents known to be used in sustained release pharmaceutical dosage unit forms" (col. 1, lines 54-56) and according to the prior art '359 or '452 and '871 other known sustained/controlled release excipients besides PVP and carboxyvinylpolymer include specifically and preferably HPMC in a combination with sodium alginate and alginic acid (see for example cited '359 [0038-0043]). Simple substitution by one of ordinary skill in the art of the sustained

release excipients of '473 for other specific sustained release excipients of '359 or '452 and '871 would yield predictable results (see MPEP 2141). Further the Examiner respectfully points out HPMC, alginic acid and sodium alginate are preferred according to '359 or '452 and '871 over the disclosed PVP and carboxyvinylpolymers of '359 and '472 and as such it would be obvious to substitute the preferred excipients of '359 or '452 and '871 into the composition of '473 with predictable results. What Appellants' mere arguments have not demonstrated is that such a substitution is unpredictable or that the instant claimed combination of sustained release excipients provide an unexpected result over other unclaimed sustained release excipients via factual evidence, side-by-side comparison, etc. Absent a showing of unexpected results, mere argument by counsel is not persuasive (see MPEP 716.01).

(B) Appellants further argue that the prior art does not teach "HPMC plus alginic acid and sodium alginate" and underlines "or" in each reference cited on page 13-14 of the brief with respect to alginic acid "or" sodium alginate regarding '359 or '452 and '871. The Examiner respectfully points out that '359 teaches known hydrophilic polymeric substances capable of providing controlled release include HPMC, alginic acid and derivatives (e.g., sodium alginate) [0038] and further goes on to state that the hydrophilic polymeric substances in the active layer comprise both controlled release polymers and viscosity-increasing polymers and preferably the active layer comprises (a) HPMC and (b) alginic acid, sodium alginate, etc. The citation includes plural not singular language and the phrase "one or more of the following" is also used in the single sentence bridging [0041-0043] which requires both (a) and (b) components

above, which the Examiner interprets as one or more of (a) and one or more of (b) since it is in a single sentence that comprises both (a) and (b). Furthermore, '452 teaches the combination of HPMC and alginic acid salts (i.e., sodium alginate) and mixtures thereof in combination with '871 teaches that a single sustained release carrier can be replaced by "one or more additional sustained release polymers" such as sodium alginate, alginic acid, etc., as long as such carrier has sustained release properties and allows release of the pharmacologically active ingredient from the formulation over a period of time greater than that for immediate release tablet can be present (col. 4, lines 5-18). Again, reiterating that a mixture of the sustained/controlled release polymers known to include HPMC in combination with alginic acid and sodium alginate can be present in the sustained/controlled release active layer according to the rejection of record '473 in view of '359 or '452 and '871. Appellants argue that such a substitution to '473 is "cherry-picking", "would render its invention inoperable" and that "one would not replace "necessary" ingredients". The Examiner acknowledges that the function of the PVP and carboxyvinyl polymer in the '473 "in order to achieve sustained release pharmaceutical[s]" is "necessary" but the function alone, not the compounds themselves (brief, page 15, top paragraph), as the prior art clearly teaches that various hydrophilic polymers are known as sustained/controlled release polymers and that preferred combinations include HPMC with "one or more" alginic acid and sodium alginate (as detailed above). The Examiner does not agree that such a substitution "would render its invention inoperable" and the prior art does not support that "necessary" means "should not be replaced" (brief pg. 14 (bottom)-15), rather the teaching of the prior art is

that at the time the invention was made there are known equivalent sustained/controlled release polymers disclosed and taught to be preferred namely combinations of HPMC, alginic acid and sodium alginate and simple substitution of these into the product of '473 (for the same function as PVP and carboxyvinyl polymer i.e., "in order to achieve sustained release pharmaceutical[s]") by one of ordinary skill in the art who is not an automaton would be obvious and yield predictable results of a sustained/rapid release oral dosage form of nitrofurantoin.

(C) Appellants also argue that instant claims 17-26, 30 and 37 claimed weight percent for: i) hypromellose (i.e., HPMC), ii) alginic acid and iii) sodium alginate are not taught as '473 does not teach hypromellose, alginic acid and sodium alginate "nor does it teach that the same weight percents may be universally used without regard to ingredient". The Examiner respectfully points out that '473 is not relied upon alone in the rejection and that while it teaches the sustained release excipients of '473 are included "in amount of 5-86% and 4-40%, etc. (col. 7, lines 5-7 and col. 8, lines 29-30)" in view of '359 (for example discussed above) sustained/controlled release excipients such as PVP, carboxyvinyl polymers, alginic acid and sodium alginate and preferably HPMC are included in the active layer from 1-75% by weight and preferably 5-65% by weight [0038, 0046]. '359 goes on to teach preferably 40-63% by weight specifically for HPMC and the viscosity increasing polymers (i.e. alginic acid and sodium alginate) 3-20% by weight which all overlap with the instant claimed weight % [0046]. As such the Examiner respectfully points out that the same sustained release components are overlapping from '473 to '359 as are the disclosed weight percents. Thus it does indeed

appear that the prior art combination recognizes 'universally' overlapping % weight for sustained release polymers in fact 5-86% and 4-40% of '473 is almost completely overlapping with the 1-75% and 5-65% of '359.

(D) Appellants also argue that claims "50-60 are directed to a method of preparing a formulation…[and] the Examiner has not made out a prima facie case of obviousness relating to a method for preparing a formulation". The Examiner respectfully points out that claims 50-60 stand properly rejected: specifically instant claims 50-52 and 54-60 are taught by '473 teaches that the components are "particulate mixtures" such as powders, granules, etc. (col. 3, lines 46-47), i) a sustained release mixture of nitrofurantoin monohydrate with the sustained release polymer (first particulate) which are uniformly mixed together with talc and zinc stearate, a second particulate mixture of macrocrystalline nitrofurantoin preferably mixed with any other pharmaceutical carriers can be added to the layers to aid in the flow of the particulate mixture into the dosage form for rapid release (col. 8, lines 47-67) and that the first and second components can be layered or enclosed in smaller units within the capsule shell containing the entire dosage form (abstract, col. 4, lines 1-19; col. 6, lines 22-26; col. 9, lines 41-col. 10, lines 30; Example 1) in view of '359 or '452 and '871 which teach known formulations for oral dosage forms include tablets and capsules (instant claim 53; as detailed above) and known sustained release polymers are preferably HPMC, alginic acid and sodium alginate and simple substitution for the sustained release polymers and/or tablet form for the sustained release polymers and/or capsule of '473 is within the purview of the skilled artisan and would yield predictable results.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

The following ground(s) of rejection are applicable to the appealed claims:

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Bethany Barham

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